TITLE OF THE INVENTION
7 AND 8 MEMBERED HETEROCYCLIC CYCLOPENTYL BENZYLAMIDE MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

BACKGROUND OF THE INVENTION

The chemokines are a family of small (70-120 amino acids), proinflammatory cytokines, with potent chemotactic activities. Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract various cells, such as monocytes, macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation (reviewed in Schall, Cytokine, 3, 165-183 (1991) and Murphy, Rev. Immun., 12, 593-633 (1994)). These molecules were originally defined by four conserved cysteines and divided into two subfamilies based on the arrangement of the first cysteine pair. In the CXC-chemokine family, which includes IL-8, GROα, NAP-2 and IP-10, these two cysteines are separated by a single amino acid, while in the CC-chemokine family, which includes RANTES, MCP-1, MCP-2, MCP-3, MIP-1α, MIP-1ß and eotaxin, these two residues are adjacent.

The α-chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils, whereas β-chemokines, such as RANTES, MIP-1α, MIP-1β, monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin are chemotactic for macrophages, monocytes, T-cells, eosinophils and basophils (Deng, et al., Nature, 381, 661-666 (1996)).

The chemokines are secreted by a wide variety of cell types and bind to specific G-protein coupled receptors (GPCRs) (reviewed in Horuk, Trends Pharm. Sci., 15, 159-165 (1994)) present on leukocytes and other cells. These chemokine receptors form a sub-family of GPCRs, which, at present, consists of fifteen characterized members and a number of orphans. Unlike receptors for promiscuous chemoattractants such as C5a, fMLP, PAF, and LTB4, chemokine receptors are more selectively expressed on subsets of leukocytes. Thus, generation of specific chemokines provides a mechanism for recruitment of particular leukocyte subsets.

On binding their cognate ligands, chemokine receptors transduce an intracellular signal though the associated trimeric G protein, resulting in a rapid increase in intracellular calcium concentration. There are at least seven human chemokine receptors that bind or respond to β-chemokines with the following characteristic pattern: CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1α, MIP-1β, MCP-3, RANTES] (Ben-Barruch, et al., J. Biol. Chem., 270, 22123-22128 (1995); Beote, et al, Cell, 72, 415-425 (1993)); CCR-2A and CCR-2B (or "CKR-2A"/"CKR-2A" or "CC-CKR-2A"/"CC-CKR-2A") [MCP-1, MCP-2, MCP-3, MCP-4]; CCR-3 (or "CKR-3" or "CC-CKR-3") [Eotaxin, Eotaxin 2, RANTES, MCP-2, MCP-3] (Rollins, et al.,

Blood, 90, 908-928 (1997)); CCR-4 (or "CKR-4" or "CC-CKR-4") [MIP-1α, RANTES, MCP-1] (Rollins, et al., Blood, 90, 908-928 (1997)); CCR-5 (or "CKR-5" or "CC-CKR-5") [MIP-1α, RANTES, MIP-1β] (Sanson, et al., Biochemistry, 35, 3362-3367 (1996)); and the Duffy blood-group antigen [RANTES, MCP-1] (Chaudhun, et al., J. Biol. Chem., 269, 7835-7838 (1994)). The β-chemokines include eotaxin, MIP ("macrophage inflammatory protein"), MCP ("monocyte chemoattractant protein") and RANTES ("regulation-upon-activation, normal T expressed and secreted") among other chemokines.

Chemokine receptors, such as CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR-4, have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases, including asthma, rhinitis and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Humans who are homozygous for the 32-basepair deletion in the CCR-5 gene appear to have less susceptibility to rheumatoid arthritis (Gomez, et al., Arthritis & Rheumatism, 42, 989-992 (1999)). A review of the role of eosinophils in allergic inflammation is provided by Kita, H., et al., J. Exp. Med. 183, 2421-2426 (1996). A general review of the role of chemokines in allergic inflammation is provided by Lustger, A.D., New England J. Med., 338(7), 426-445 (1998).

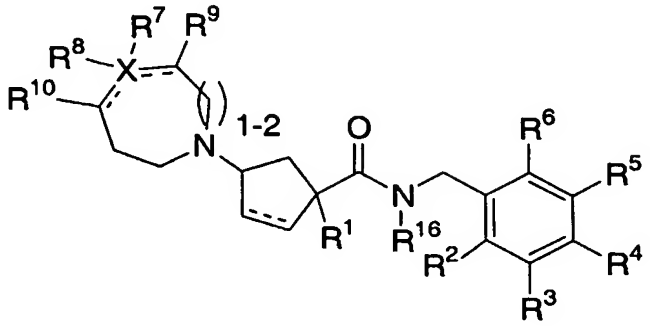
A subset of chemokines are potent chemoattractants for monocytes and macrophages. The best characterized of these is MCP-1 (monocyte chemoattractant protein-1), whose primary receptor is CCR2. MCP-1 is produced in a variety of cell types in response to inflammatory stimuli in various species, including rodents and humans, and stimulates chemotaxis in monocytes and a subset of lymphocytes. In particular, MCP-1 production correlates with monocyte and macrophage infiltration at inflammatory sites. Deletion of either MCP-1 or CCR2 by homologous recombination in mice results in marked attenuation of monocyte recruitment in response to thioglycollate injection and *Listeria monocytogenes* infection (Lu et al., J. Exp. Med., 187, 601-608 (1998); Kurihara et al. J. Exp. Med., 186, 1757-1762 (1997); Boring et al. J. Clin. Invest., 100, 2552-2561 (1997); Kuziel et al. Proc. Natl. Acad. Sci., 94, 12053-12058 (1997)). Furthermore, these animals show reduced monocyte infiltration into granulomatous lesions induced by the injection of schistosomal or mycobacterial antigens (Boring et al. J. Clin. Invest., 100, 2552-2561 (1997); Warmington et al. Am J. Path., 154, 1407-1416 (1999)). These data suggest that MCP-1-induced CCR2 activation plays a major role in monocyte recruitment to inflammatory sites, and that antagonism of this activity will produce a sufficient suppression of the immune response to produce therapeutic benefits in immunoinflammatory and autoimmune diseases.

Accordingly, agents which modulate chemokine receptors such as the CCR-2 receptor would be useful in such disorders and diseases.

In addition, the recruitment of monocytes to inflammatory lesions in the vascular wall is a major component of the pathogenesis of atherogenic plaque formation. MCP-1 is produced and secreted by endothelial cells and intimal smooth muscle cells after injury to the vascular wall in hypercholesterolemic conditions. Monocytes recruited to the site of injury infiltrate the vascular wall and differentiate to foam cells in response to the released MCP-1. Several groups have now demonstrated that aortic lesion size, macrophage content and necrosis are attenuated in MCP-1 -/- or CCR2 -/- mice backcrossed to APO-E -/-, LDL-R -/- or Apo B transgenic mice maintained on high fat diets (Boring et al. Nature, 394, 894-897 (1998); Gosling et al. J. Clin. Invest., 103, 773-778 (1999)). Thus, CCR2 antagonists may inhibit atherosclerotic lesion formation and pathological progression by impairing monocyte recruitment and differentiation in the arterial wall.

SUMMARY OF THE INVENTION

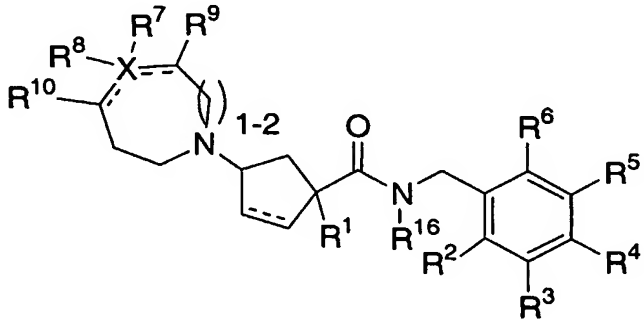
The present invention is further directed to compounds of the formula:



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{16} are as defined herein, which are modulators of chemokine receptor activity and are useful in the prevention or treatment of certain inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which chemokine receptors are involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

wherein:

X is O, N, S, SO_2 or C;

R^1 is selected from:

hydrogen, -C_{1-6}alkyl, -C_{0-6}alkyl-O-C_{1-6}alkyl, -C_{0-6}alkyl-S-C_{1-6}alkyl, -(C_{0-6}alkyl)-(C_{3-7}cycloalkyl)-(C_{0-6}alkyl), hydroxy, heterocycle, -CN, -$NR^{12}R^{12}$, -$NR^{12}COR^{13}$, -$NR^{12}SO_2R^{14}$, -$NR^{12}SO_2NR^{12}$, -COR^{11}, -$CONR^{12}R^{12}$, and phenyl, where:

said alkyl and cycloalkyl groups are unsubstituted or substituted with 1-7 substituents independently selected from: halo, hydroxy, -O-C_{1-3}alkyl, trifluoromethyl, C_{1-3}alkyl, -O-C_{1-3}alkyl, -COR^{11}, -SO_2R^{14},-$NHCOCH_3$, -$NHSO_2CH_3$, -heterocycle, =O, and -CN,

said phenyl and heterocycle groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

R^{11} is selected from: hydroxy, hydrogen, C_{1-6} alkyl, -O- C_{1-6}alkyl, benzyl, phenyl, C_{3-6} cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl, and trifluoromethyl,

R^{12} is independently selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{3-6} cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl, and trifluoromethyl,

R^{13} is selected from: hydrogen, C_{1-6} alkyl, -O-C_{1-6}alkyl, benzyl, phenyl, C_{3-6} cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl, and trifluoromethyl, and

R^{14} is selected from: hydroxy, C_{1-6} alkyl, -O-C_{1-6}alkyl, benzyl, phenyl, C_{3-6} cycloalkyl where the alkyl, phenyl, benzyl, and cycloalkyl groups can be unsubstituted or substituted with 1-3 independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, -CO_2H, -CO_2-C_{1-6} alkyl, and trifluoromethyl;

R^2 is selected from:

(a) hydrogen,

(b) C_{1-3}alkyl, unsubstituted or substituted with 1-3 fluoro,
(c) -O-C_{1-3}alkyl, unsubstituted or substituted with 1-3 fluoro,
(d) hydroxy,
(e) chloro,
(f) fluoro,
(g) bromo, and
(h) phenyl;

R^3 is selected from:

(a) hydrogen,
(b) hydroxy,
(c) halo,
(d) C_{1-3}alkyl unsubstituted or substituted with 1-6 substituents independently selected from: fluoro, hydroxy, and $-COR^{11}$,
(e) $-NR^{12}R^{12}$,
(f) $-COR^{11}$,
(g) $-CONR^{12}R^{12}$,
(h) $-NR^{12}COR^{13}$,
(i) $-OCONR^{12}R^{12}$,
(j) $-NR^{12}CONR^{12}R^{12}$,
(k) -heterocycle,
(l) -CN,
(m) $-NR^{12}-SO_2-NR^{12}R^{12}$,
(n) $-NR^{12}-SO_2-R^{14}$,
(o) $-SO_2-NR^{12}R^{12}$ and
(p) nitro;

R^4 is selected from:

(a) hydrogen,
(b) C_{1-3}alkyl, unsubstituted or substituted with 1-3 fluoro,
(c) -O-C_{1-3}alkyl, unsubstituted or substituted with 1-3 fluoro,
(d) hydroxy,
(e) chloro,
(f) fluoro,
(g) bromo, and
(h) phenyl;

R^5 is selected from:

(a) C_{1-6}alkyl, unsubstituted or substituted with 1-6 fluoro, hydroxyl, or both,
(b) -O-C_{1-6}alkyl, unsubstituted or substituted with 1-6 fluoro,

(c) -CO-C_{1-6}alkyl,unsubstituted or substituted with 1-6 fluoro,
(d) -S-C_{1-6}alkyl, unsubstituted or substituted with 1-6 fluoro,
(e) -pyridyl, unsubstituted or substituted with one or more substituents selected from: halo, trifluoromethyl, C_{1-4}alkyl, and COR^{11},
(f) fluoro,
(g) chloro,
(h) bromo,
(i) -C_{4-6}cycloalkyl, unsubstituted or substituted with 1-6 fluoro,
(j) -O-C_{4-6}cycloalkyl, unsubstituted or substituted with 1-6 fluoro,
(k) phenyl, unsubstituted or substituted with one or more substituents selected from: halo, trifluoromethyl, C_{1-4}alkyl, and COR^{11},
(l) -O-phenyl, unsubstituted or substituted with one or more substituents selected from: halo, trifluoromethyl, C_{1-4}alkyl, and COR^{11},
(m) -heterocycle,
(n) -CN, and
(o) $-COR^{11}$;

R^6 is selected from:

(a) hydrogen,
(b) C_{1-3}alkyl, unsubstituted or substituted with 1-3 fluoro,
(c) -O-C_{1-3}alkyl, unsubstituted or substituted with 1-3 fluoro,
(d) hydroxy,
(e) chloro,
(f) fluoro,
(g) bromo, and
(h) phenyl;

R^7 is selected from:

(a) hydrogen,
(b) (C_{0-6}alkyl)-phenyl,
(c) (C_{0-6}alkyl)-heterocycle,
(d) (C_{0-6}alkyl)-C_{3-7}cycloalkyl ,
(e) (C_{0-6}alkyl)-COR^{11},
(f) (C_{0-6}alkyl)-(alkene)-COR^{11},
(g) (C_{0-6}alkyl)-SO_3H,
(h) (C_{0-6}alkyl)-W-C_{0-4}alkyl, where W is selected from: a single bond, -O-, -S-, -SO-, -SO_2-, -CO-, -CO_2-, -$CONR^{12}$- and $-NR^{12}$-,
(i) (C_{0-6}alkyl)-CON R^{12}-phenyl,
(j) (C_{0-6}alkyl)-CON R^{15}-V-CO R^{11}, where V is selected from C_{1-6}alkyl or phenyl, and

(k) nothing, when X is O, S, or SO_2;

where:

R^{15} is hydrogen or C_{1-4}alkyl, or where R^{15} is joined via a 1-5 carbon tether to one of the carbons of V to form a ring,

C_{0-6}alkyl is unsubstituted or substituted with 1-5 substituents, where the substituents are independently selected from:

(a) halo,
(b) hydroxy,
(c) -C_{0-6}alkyl
(d) -O-C_{1-3}alkyl,
(e) trifluoromethyl, and
(f) -C_{0-2}alkyl-phenyl,

phenyl, heterocycle, cycloalkyl, and C_{0-4}alkyl is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) -O-C_{1-3} alkyl,
(f) - C_{0-3}-COR^{11},
(g) -CN,
(h) -$NR^{12}R^{12}$,
(i) -$CONR^{12}R^{12}$, and
(j) - C_{0-3}-heterocycle,

where the phenyl and heterocycle may be fused to another heterocycle, which itself may be unsubstituted or substituted with 1-2 substituents independently selected from hydroxy, halo, -CO R^{11}, and –C_{1-3}alkyl, and where

alkene is unsubstituted or substituted with 1-3 substituents which are independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) C_{1-3}alkyl,
(d) phenyl, and
(e) heterocycle;

R^8 is selected from:

(a) hydrogen,
(b) nothing when X is either O, S, SO_2 or N or when a double bond joins the carbons to which R^7 and R^{10} are attached,
(c) hydroxy,
(d) C_{1-6}alkyl,
(e) C_{1-6}alkyl-hydroxy,
(f) -O-C_{1-3}alkyl,
(g) -COR^{11},
(h) -$CONR^{12}R^{12}$, and
(i) -CN;

or where R^7 and R^8 may be joined together to form a ring which is selected from:

(a) 1H-indene,
(b) 2,3-dihydro-1H-indene,
(c) 2,3-dihydro-benzofuran,
(d) 1,3-dihydro-isobenzofuran,
(e) 2,3-dihydro-benzothiofuran,
(f) 1,3-dihydro-isobenzothiofuran,
(g) 6*H*-cyclopenta[*d*]isoxazol-3-ol
(h) cyclopentane, and
(i) cyclohexane,

where the ring formed may be unsubstituted or substituted with 1-5 substituents independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) -O-C_{1-3}alkyl,
(f) -C_{0-3}-COR^{11},
(g) -CN,
(h) -$NR^{12}R^{12}$,
(i) -$CONR^{12}R^{12}$, and
(j) - C_{0-3}-heterocycle,

or where R^7 and R^9 or R^8 and R^{10} may be joined together to form a ring which is phenyl or heterocycle, wherein the ring is unsubstituted or substituted with 1-7 substituents independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) -O-C_{1-3}alkyl,
(f) -COR^{11},
(g) -CN,
(h) -$NR^{12}R^{12}$, and
(i) -$CONR^{12}R^{12}$;

R^9 and R^{10} are independently selected from:

(a) hydrogen,
(b) hydroxy,
(c) C_{1-6}alkyl,
(d) C_{1-6}alkyl-COR^{11},
(e) C_{1-6}alkyl-hydroxy,
(f) -O-C_{1-3}alkyl,
(g) =O, when R^9 or R^{10} is connected to the ring via a double bond
(h) halo;

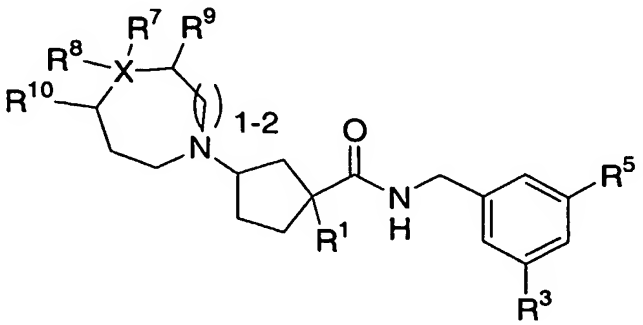
R^{16} selected from:

(a) hydrogen,
(b) phenyl,
(c) C_{1-6}alkyl which may be substituted or unsubstituted with 1-6 of the following substituents: -COR^{11}, hydroxy, fluoro, chloro, -O-C_{1-3} alkyl;

the dashed line represents a single or a double bond;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

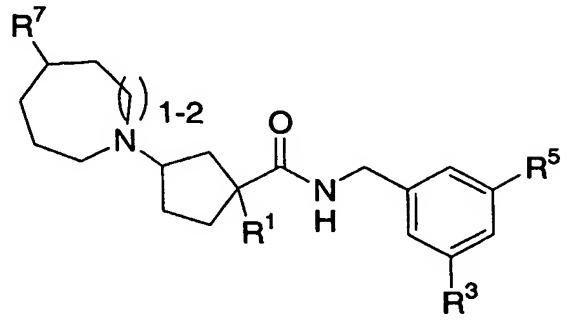
Other compounds of the present invention include compounds of formula Ia:



Ia

wherein R^1, R^3, R^5, R^7, R^8, R^9, and R^{10} are defined herein.

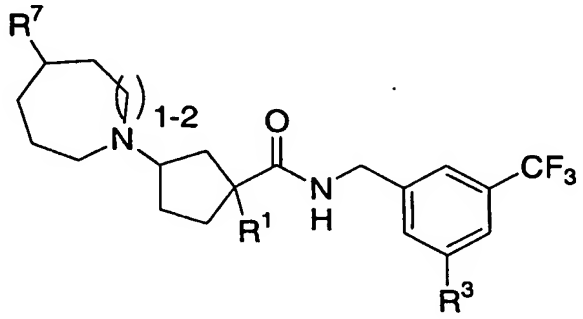
Additional compounds of the present invention include compounds of formula Ib:



Ib

wherein R^1, R^3, R^5, and R^7 are defined herein.

More compounds of the present invention include compounds of the formula Ic:



Ic

wherein R^1, R^3, and R^7 are defined herein.

Embodiments of the present invention include those wherein X is N, O, or C.

Embodiments of the present invention also include those wherein R^1 is selected from:

-C_{1-6}alkyl, -C_{0-6}alkyl-O-C_{1-6}alkyl, heterocycle, and
-(C_{0-6}alkyl)-(C_{3-7}cycloalkyl)-(C_{0-6}alkyl),

where the alkyl, heterocycle, and the cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from:

(a) halo,
(b) hydroxy,
(c) -O-C_{1-3}alkyl,
(d) trifluoromethyl,
(f) C_{1-3}alkyl,
(g) -O-C_{1-3}alkyl,
(h) -COR^{11},
(i) -CN,
(j) -$NR^{12}R12$,
(k) -$CONR^{12}R12$, and
(j) -$NCOR^{13}$.

Further, the present invention includes embodiments wherein R^1 is selected from:

-C_{1-6}alkyl, which is unsubstituted or substituted with 1-6 substituents where the substituents are independently selected from:

(a) halo,
(b) hydroxy,
(c) -O-C_{1-3}alkyl,
(d) trifluoromethyl, and
(e) -COR^{11};

-C_{0-6}alkyl-O-C_{1-6}alkyl-, which is unsubstituted or substituted with 1-6 substituents where the substituents are independently selected from:

(a) halo,
(b) trifluoromethyl, and
(c) -COR^{11};

-(C_{3-5}cycloalkyl)-(C_{0-6}alkyl), which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(a) halo,
(b) hydroxy,
(c) -O-C_{1-3}alkyl,
(d) trifluoromethyl, and
(e) -COR^{11}; and

heterocycle unsubstituted or substituted with $-NCOR^{13}$ or $-NR^{12}R^{12}$.

The invention includes embodiments wherein R^1 is selected from:

(a) C_{1-6}alkyl,
(b) C_{1-6}alkyl substituted with hydroxy,
(c) C_{1-6}alkyl substituted with 1-6 fluoro, and
(d) thiazole, unsubstituted or substituted with $-NHCOR^{13}$.

The invention also includes embodiments wherein R^1 is selected from:

(a) $-CH(CH_3)_2$,
(b) $-C(OH)(CH_3)_2$,
(c) $-CH(OH)CH_3$,
(d) $-CH_2CF_3$, and
(e) -thiazole (bonded to the core at the 4 position of the thiazole ring), unsubstituted or substituted with $-NHCOCH_3$ at the 2 position of the thiazole ring.

In certain embodiments of the present invention R^2 is hydrogen.

In certain embodiments of the present invention R^3 is selected from:

(a) hydrogen
(b) halo
(c) hydroxy
(d) C_{1-3}alkyl, where the alkyl is unsubstituted or substituted with 1-6 substituents independently selected from: fluoro, and hydroxy,
(e) $-COR^{11}$,
(f) $-CONR^{12}R^{12}$,
(g) -heterocycle,
(h) $-NR^{12}-SO_2-NR^{12}R^{12}$,
(i) $-NR^{12}-SO_2-R^{14}$,
(j) $-SO_2-NR^{12}R^{12}$,
(k) -nitro, and
(l) $-NR^{12}R^{12}$.

In certain other embodiments of the present invention R^3 is selected from:

(a) hydrogen,
(b) fluoro, and
(c) trifluoromethyl.

In still other embodiments of the present invention R^3 is selected from fluoro andtrifluoromethyl.

In certain embodiments of the present invention R^4 is hydrogen.

In certain embodiments of the present invention R^5 is selected from:

(a) C_{1-6}alkyl substituted with 1-6 fluoro,
(b) -O-C_{1-6}alkyl substituted with 1-6 fluoro,
(c) chloro,
(d) bromo, and
(e) phenyl.

In certain other embodiments of the present invention R^5 is selected from:

(a) trifluoromethyl,
(b) trifluoromethoxy,
(c) chloro,
(d) bromo, and
(e) phenyl.

In still other embodiments of the present invention R^5 is trifluoromethyl.

In certain embodiments of the present invention R^6 is hydrogen.

In certain embodiments of the present invention R^7 is selected from phenyl, heterocycle, C_{3-7}cycloalkyl, C_{1-6}alkyl, $-COR^{11}$, and -CONH-V-COR^{11},

where V is selected from C_{1-6}alkyl or phenyl, and

where the phenyl, heterocycle, C_{3-7}cycloalkyl, and C_{1-6}alkyl is unsubstituted or substituted with 1-5 substituents independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) -O-C_{1-3}alkyl,
(f) $-COR^{11}$,
(g) -CN,
(h) -heterocycle, and
(i) $-CONR^{12}R^{12}$.

In certain other embodiments of the present invention R^7 is selected from phenyl, heterocycle, C_{1-4}alkyl, $-COR^{11}$, and -CONH-V-COR^{11},

where V is selected from C_{1-6}alkyl or phenyl, and

where the phenyl, heterocycle, and C_{1-4}alkyl is unsubstituted or substituted with 1-3 substituents independently selected from:

(a) halo,
(b) hydroxy,
(c) C_{1-3}alkyl,
(d) -O-C_{1-3}alkyl,
(e) -COR^{11},and
(f) -heterocycle.

In still other embodiments of the present invention R^7 is selected from:

(a) hydrogen,
(b) -COR^{11},
(c) $-CONHCH_3$,
(d) phenyl,
(e) heterocycle,

In certain embodiments of the present invention, when X is C, R^8 is selected from:

(a) hydrogen,
(b) hydroxy,
(c) -CN, and
(d) -F.

In certain other embodiments of the present invention R^8 is hydrogen.

In still other embodiments of the present invention R^7 and R^8 may be joined together to form a ring which is selected from 1H-indene and 2,3-dihydro-1H-indene,

where the ring formed may be unsubstituted or substituted with 1-3 substituents independently selected from:

(a) halo,
(b) hydroxy,
(c) C_{1-3}alkyl,
(d) -O-C_{1-3}alkyl,
(e) -COR^{11}, and
(f) -heterocycle.

In certain embodiments of the present invention R^9 and R^{10} are independently selected from:

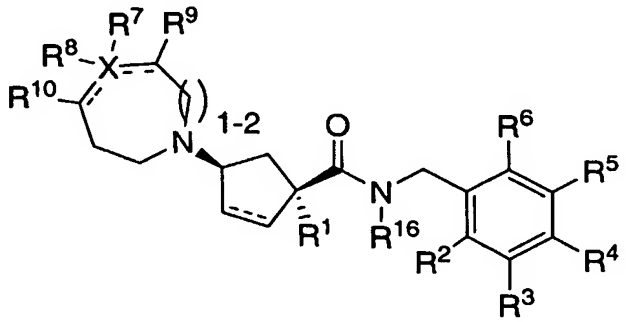
(a) hydrogen,
(b) hydroxy,
(c) -CH_3,
(d) -O-CH_3, and
(e) =O (where R^9 and/or R^{10} are joined to the ring via a double bond).

In certain other embodiments of the present invention R^9 and R^{10} are hydrogen.

In certain embodiments of the present invention R^{16} is hydrogen.

Representative compounds of the present invention include those presented in the Examples and pharmaceutically acceptable salts and individual diastereomers thereof.

The compounds of the instant invention have at least 2 asymmetric centers at the 1 and 3 positions of the cyclopentyl ring. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The absolute configurations of selected compounds of this orientation, with substituents on the cyclopentyl ring (amide and amine units), are as depicted below:



The independent syntheses of diastereomers and enantiomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

The independent syntheses of diastereomers and enantiomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

As appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo. Similarly, C_{1-8}, as in C_{1-8}alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbons in a linear or branched arrangement, such that C_{1-8}alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl, heptyl and octyl. Likewise, C_0, as in C_0alkyl is defined to identify the presence of a direct covalent bond. The term "heterocycle" as used herein is intended to include the following groups: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoim idazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or

the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be prepared from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Suitable salts are found, e.g. in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

Specific compounds within the present invention include a compound which selected from the group consisting of: the title compounds of the Examples; and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of modulating chemokine receptor activity in a patient in need of such modulation comprising the administration of an effective amount of the compound.

The present invention is directed to the use of the foregoing compounds as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, in particular CCR-2.

The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for chemokine binding as disclosed by Van Riper, et al., J. Exp. Med., 177, 851-856 (1993) which may be readily adapted for measurement of CCR-2 binding.

Receptor affinity in a CCR-2 binding assay was determined by measuring inhibition of ^{125}I-MCP-1 to the endogenous CCR-2 receptor on various cell types including monocytes, THP-1 cells, or after heterologous expression of the cloned receptor in eukaryotic cells. The cells were suspended in binding buffer (50 mM HEPES, pH 7.2, 5 mM $MgCl_2$, 1 mM $CaCl_2$, and 0.50% BSA or 0.5% human serum) and added to test compound or DMSO and ^{125}I-

MCP-1 at room temperature for 1 h to allow binding. The cells were then collected on GFB filters, washed with 25 mM HEPES buffer containing 500 mM NaCl and cell bound ^{125}I-MCP-1 was quantified.

In a chemotaxis assay chemotaxis was performed using T cell depleted PBMC isolated from venous whole or leukophoresed blood and purified by Ficoll-Hypaque centrifugation followed by rosetting with neuraminidase-treated sheep erythrocytes. Once isolated, the cells were washed with HBSS containing 0.1 mg/ml BSA and suspended at $1x10^7$ cells/ml. Cells were fluorescently labeled in the dark with 2 μM Calcien-AM (Molecular Probes), for 30 min at 37° C. Labeled cells were washed twice and suspended at $5x10^6$ cells/ml in RPMI 1640 with L-glutamine (without phenol red) containing 0.1 mg/ml BSA. MCP-1 (Peprotech) at 10 ng/ml diluted in same medium or medium alone were added to the bottom wells (27 μl). Monocytes (150,000 cells) were added to the topside of the filter (30 μl) following a 15 min preincubation with DMSO or with various concentrations of test compound. An equal concentration of test compound or DMSO was added to the bottom well to prevent dilution by diffusion. Following a 60 min incubation at 37° C, 5 % CO_2, the filter was removed and the topside was washed with HBSS containing 0.1 mg/ml BSA to remove cells that had not migrated into the filter. Spontaneous migration (chemokinesis) was determined in the absence of chemoattractant

In particular, the compounds of the following examples had activity in binding to the CCR-2 receptor in the aforementioned assays, generally with an IC_{50} of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

Mammalian chemokine receptors provide a target for interfering with or promoting eosinophil and/or leukocyte function in a mammal, such as a human. Compounds which inhibit or promote chemokine receptor function, are particularly useful for modulating eosinophil and/or leukocyte function for therapeutic purposes. Accordingly, compounds which inhibit or promote chemokine receptor function would be useful in treating, preventing, ameliorating, controlling or reducing the risk of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as

rheumatoid arthritis and atherosclerosis, and further, chronic obstructive pulmonary disease, and multiple schlerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation. As a result, one or more inflammatory processes, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the compounds of the present invention. In a certain embodiment, the disease or condition is one in which the actions of leukocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

Diseases or conditions of humans or other species which can be treated with inhibitors of chemokine receptor function, include, but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic diseases such as asthma, particularly bronchial asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersentitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and

inflammatory dermatoses such an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myositis, eosinophilic fasciitis; and cancers, including cancers with leukocyte infiltration of the skin or organs and other cancers. Inhibitors of chemokine receptor function may also be useful in the treatment and prevention of stroke (Hughes et al., *Journal of Cerebral Blood Flow & Metabolism,* **22**:308–317, 2002, and Takami et al., *Journal of Cerebral Blood Flow & Metabolism,* **22**:780–784, 2002), neurodegenerative conditions including but not limited to Alzheimer's disease, amyotrophic lateral sclerosis (ALS) and Parkinson's disease, obesity, type II diabetes, neuropathic and inflammatory pain, and Guillain Barre syndrome. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis and chronic obstructive pulmonary disease.

Diseases or conditions of humans or other species, which can be treated with modulators of chemokine receptor function, include or involve but are not limited to: immunosuppression, such as that in individuals with immunodeficiency syndromes such as AIDS or other viral infections, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due to congenital deficiency in receptor function or other causes; and infections diseases, such as parasitic diseases, including, but not limited to helminth infections, such as nematodes (round worms), (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis), trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis), visceral worms, visceral larva migraines (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki sp., Phocanema sp.), and cutaneous larva migraines (Ancylostona braziliense, Ancylostoma caninum).

In addition, treatment of the aforementioned inflammatory, allergic, infectious and autoimmune diseases can also be contemplated for agonists of chemokine receptor function if one contemplates the delivery of sufficient compound to cause the loss of receptor expression on cells through the induction of chemokine receptor internalization or delivery of compound in a manner that results in the misdirection of the migration of cells.

The compounds of the present invention are accordingly useful in treating, preventing, ameliorating, controlling or reducing the risk of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic conditions, atopic conditions, as well as autoimmune pathologies. In a specific embodiment, the present invention is directed to the use of the subject compounds for treating, preventing, ameliorating, controlling or reducing the risk of autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis and multiple schlerosis.

In another aspect, the instant invention may be used to evaluate putative specific agonists or antagonists of chemokine receptors, including CCR-2. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds that modulate the activity of chemokine receptors. For example, the compounds of this invention are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors, including CCR-2. As appreciated in the art, thorough evaluation of specific agonists and antagonists of the above chemokine receptors has been hampered by the lack of availability of non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. Thus the compounds of this invention are commercial products to be sold for these purposes.

The present invention is further directed to a method for the manufacture of a medicament for modulating chemokine receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The present invention is further directed to the use of the present compounds in treating, preventing, ameliorating, controlling or reducing the risk of infection by a retrovirus, in particular, herpes virus or the human immunodeficiency virus (HIV) and the treatment of, and delaying of the onset of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g.,

blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

In a further aspect of the present invention, a subject compound may be used in a method of inhibiting the binding of a chemokine to a chemokine receptor, such as CCR-2, of a target cell, which comprises contacting the target cell with an amount of the compound which is effective at inhibiting the binding of the chemokine to the chemokine receptor.

The subject treated in the methods above is a mammal, for instance a human being, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism, inverse agonism and/or partial agonism. In an aspect of the present invention, modulation refers to antagonism of chemokine receptor activity. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment.

As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the aforementioned conditions.

Combined therapy to modulate chemokine receptor activity for thereby treating, preventing, ameliorating, controlling or reducing the risk of inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and multiple sclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

For example, in treating, preventing, ameliorating, controlling or reducing the risk of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, biological TNF sequestrants, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention may be used. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

Examples of other active ingredients that may be combined with CCR2 antagonists, such as the CCR2 antagonists compounds of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO95/15973, WO96/01644, WO96/06108, WO96/20216, WO96/22966, WO96/31206, WO96/40781, WO97/03094, WO97/02289, WO 98/42656, WO98/53814, WO98/53817, WO98/53818,

WO98/54207, and WO98/58902; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin, EDG receptor agonists including FTY-720, and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, desloratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially CCR-1, CCR-2, CCR-3, CXCR-3, CXCR-4 and CCR-5; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, rosuvastatin, and other statins), sequestrants (cholestyramine and colestipol), cholesterol absorption inhibitors (ezetimibe), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferon beta (interferon beta-1α, interferon beta-1β); (m) preparations of glatiramer acetate;

(n) preparations of CTLA4Ig; (o) preparations of hydroxychloroquine, (p) Copaxone® and (q) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine, 6-mercaptopurine and methotrexate, leflunomide, teriflunomide, and cytotoxic and other cancer chemotherapeutic agents.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, or from about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the

desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products

of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In treating, preventing, ameliorating, controlling or reducing the risk of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.0001 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. In certain embodiments the dosage level will be about 0.0005 to about 400 mg/kg per day; or from about 0.005 to about 300 mg/kg per day; or from about 0.01 to about 250 mg/kg per day, or from about 0.05 to about 100 mg/kg per day, or from about 0.5 to about 50 mg/kg per day. Within this range the dosage may be 0.0001 to 0.005, 0.005 to 0.05, 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions may be provided in the form of tablets containing 0.01 to 1000 milligrams of the active ingredient, or 0.1 to 500, 1.0 to 400, or 2.0 to 300, or 3.0 to 200, particularly 0.01, 0.05, 0.1, 1, 4, 5, 10, 15, 20, 25, 30, 50, 75, 100, 125, 150, 175, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be

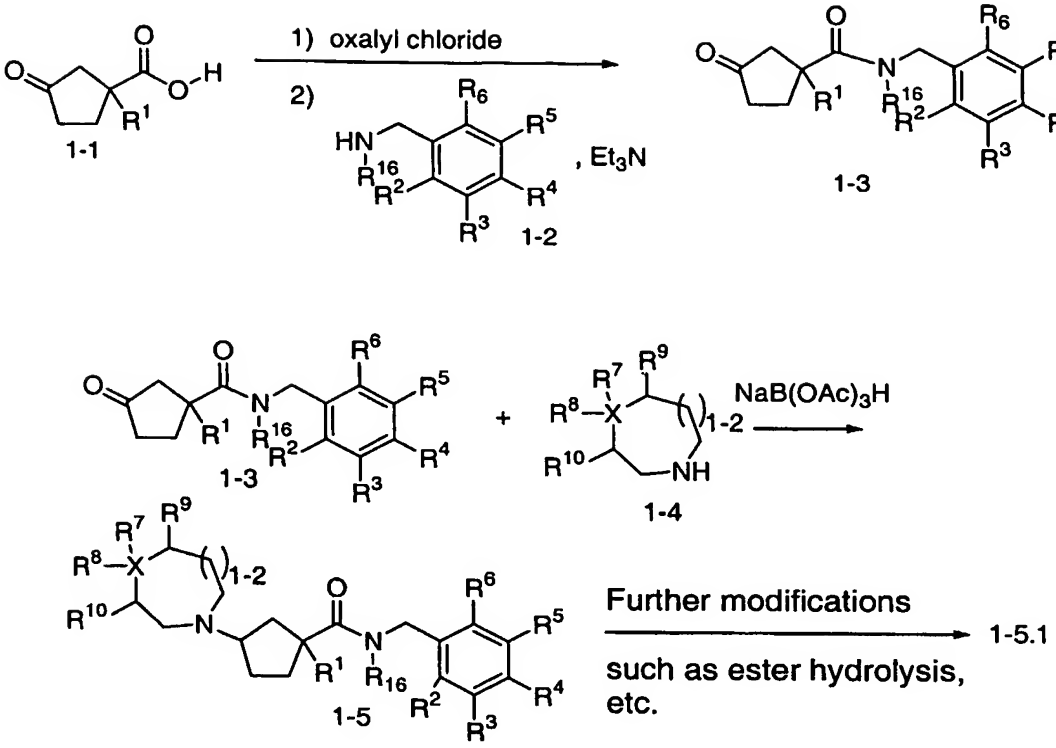
treated. The compounds may be administered on a regimen of 1 to 4 times per day, or once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made by known procedures or as illustrated.

One of the principal routes used for preparation of compounds within the scope of the instant invention which bear a 1,1,3-trisubstituted cyclopentane framework 1-5 is depicted in Scheme 1. According to this route, keto acids 1-1 (preparation described in Schemes 2A, 2B, 2C, and 2D) are coupled to amines 1-2 (either commercially available or synthesized according to literature procedures). This can be accomplished in various ways, including by first converting the acid to its acid chloride with a reagent such as oxalyl chloride, and then combining with amine 1-2 in the presence of a base such as triethylamine. Reductive amination of 1-3 with an amine 1-4 (available commercially or synthesized according to literature procedures) using, for example, $NaB(OAc)_3H$ or $NaBH_3CN$ as the reducing agent gives chemokine receptor modulators 1-5. The compounds 1-5, which can be synthesized according to the chemistry described in Scheme 1 represent stereoisomeric mixtures (Eliel, E. E., Wilen, S. H., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York). In particular, compounds 1-5 are often obtained as a mixture of cis and trans isomers. When 1-1 is a single stereoisomer only 2 possible isomers of 1-5 can result (cis and trans); these can be separated by a variety of methods, including by preparative TLC, flash chromatography, MPLC, or by HPLC using a column with a chiral stationary phase. When 1-1 is racemic, a total of at least 4 possible isomers of 1-5 can be obtained. Again, these may be separated by HPLC using a column with a chiral stationary phase, or by a combination of the methods above.

SCHEME 1



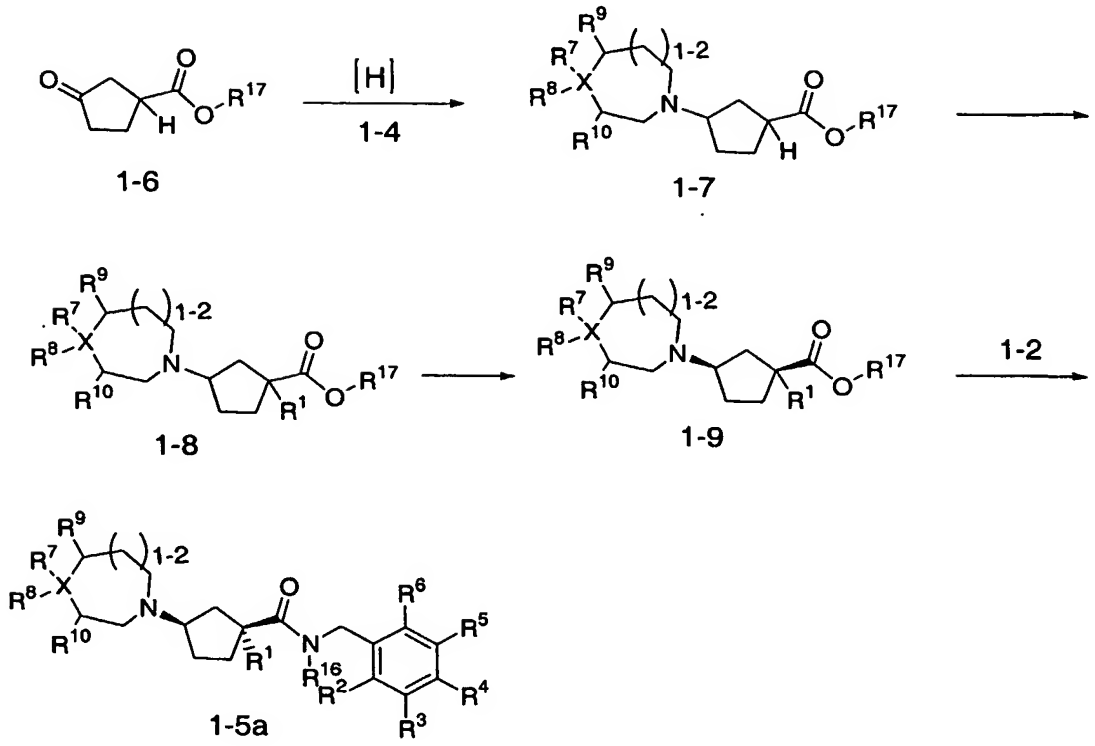
Furthermore, compounds 1-5 can themselves be modified to give new chemokine receptor modulators 1-5.1. For example, an ester functional group within a compound 1-5 can be hydrolyzed to the corresponding carboxylic acid, which also can be a chemokine receptor modulator.

As an alternate route to chemokine modulators 1-5 is shown in Scheme 1A. As depicted in this scheme, the keto-ester 1-6 could be reductively aminated with amine 1-4 to form the amino ester 1-7 under a variety of conditions, including sodium triacetoxyborohydride or sodium cyanoborohydride. Alkylation of the ester 1-7 with an alkylating agent such as an alkyl chloride, bromide or iodide in the presence of an appropriate base such as lithium bis(trimethylsilyl)amide, affords the intermediate esters 1-8. These esters formed in the above mentioned transformations represent in general a mixture of 1,3-cis- and 1,3-trans-diastereoisomers, which could be separated into respective diastereoisomeric pairs using column chromatography. A similar diastereoisomeric separation could be also accomplished later, after the esters 1-8 were hydrolytically cleaved to yield the respective acids 1-9. This hydrolysis was readily accomplished under usual conditions, including lithium, sodium or potassium hydroxide, at ambient to elevated temperatures, depending on the nature of the ester group and substituent

R^1. These diastereoisomers could be separated by crystallization from a variety of solvents, taking advantage of the finding, that the cis-diastereoisomeric acids are less soluble, when compared to their trans- epimers.

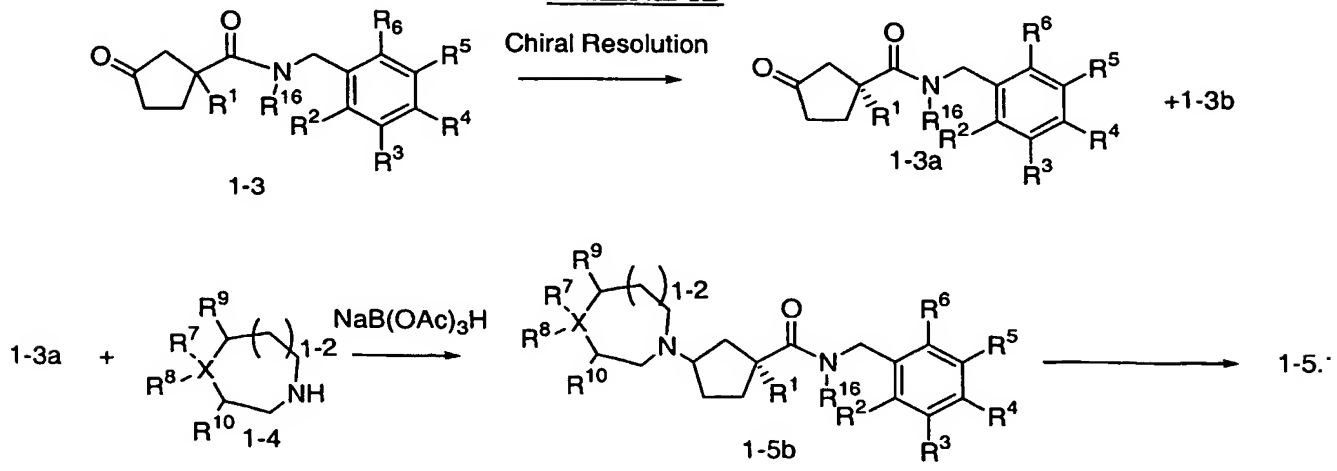
The compounds of formula 1-5a are then formed from the acids 1-9 and benzylamine derivatives 1-2 under standard amide-bond forming reaction conditions, including carbodiimide reagents, such as DCC, EDC and catalysts such as DMAP, HOAT or HOBT.

SCHEME 1A



Additionally, Intermediate 1-3 can also be resolved by Chiral HPLC to give 1-3a and 1-3b (Scheme 1B). This then would give cis/trans isomers 1-5a and 1-5b.

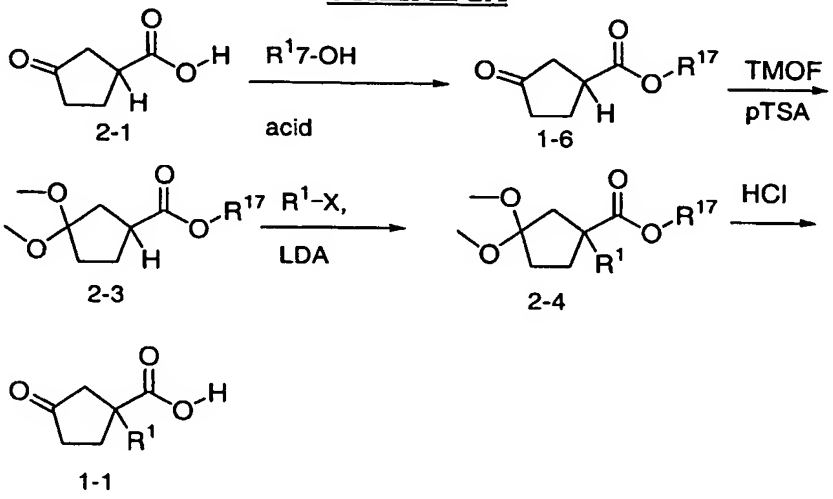
SCHEME 1B



One of the principal routes used for the preparation of Intermediate 1-1 and Intermediate 1-6 is outlined in Scheme 2A. According to this route, 3-oxocyclopentanecarboxylic acid (2-1), which

can be synthesized following a known procedure (Stetter, H., Kuhlman, H., Liebigs Ann. Chim., **1979**, 944) is esterified under standard conditions. When R^{17} represents a tert-Butyl group, the respective ester 1-6 can be prepared by reacting the appropriate alcohol, in this case tert-butanol, with acid 2-1 in the presence of sulfuric acid. Protection of the oxo-group in 2-1 can be achieved by a number of ways (Greene, T., Wuts, P. G. M., Protective Groups in Organic Chemistry, John Wiley & Sons, Inc., New York, NY 1991). The particularly suitable dimethyl acetal protecting group can be introduced using trimethyl orthoformate as a reagent in a suitable solvent such as dichloromethane and methyl alcohol in the presence of an acidic catalyst. Alternatively, in the case of R^{17} being a methyl group, the acid 2-1 can be converted to 2-3 directly by using trimethyl orthoformate and an acidic catalyst, such as para-toluenesulfonic acid. An alkylation of esters 2-3 with an alkylating agent such as an alkyl chloride, bromide or iodide in the presence of an appropriate base such as lithium diisopropylamide, produces intermediates 2-4. The ester protecting group present in 2-4 can be removed in a number of ways, depending on the nature of the ester. Methyl esters (R^{17} = methyl) can be hydrolyzed in the presence of an acid or base at ambient or elevated temperatures, whereas tert-butyl esters (R^{17} = tert-butyl) can be easily cleaved under acidic conditions. Under these conditions, the dimethyl acetal is simultaneously deprotected to give 1-1.

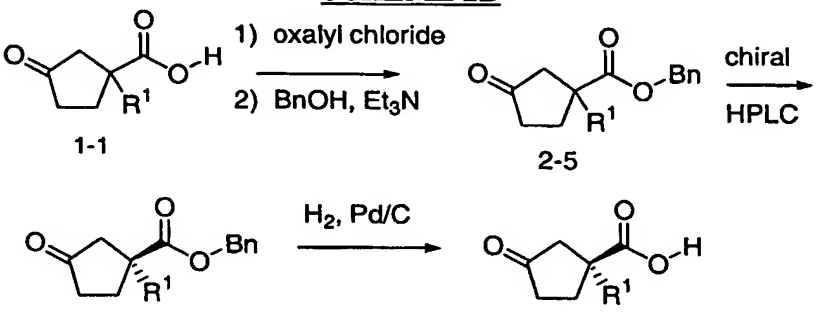
SCHEME 2A



Intermediate 1-1 can also be prepared as a single stereoisomer (1-1a) in various ways including those depicted in Schemes 2B and 2C. According to Scheme 2B, racemic 1-1

can be converted to its benzyl ester. There are many ways to effect this esterification, one of which being by a sequence involving conversion to the corresponding acid chloride with, for example oxalyl chloride, followed by treatment with benzyl alcohol in the presence of a base such as triethylamine. Then the racemic benzyl ester 2-5 can be separated by chiral preparative HPLC to give 2-5a as a single stereoisomer. Removal of the benzyl group to give the chiral ketoacid 1-1a can be accomplished in several ways. One convenient way is by hydrogenolysis in the presence of a catalyst such as Pd/C.

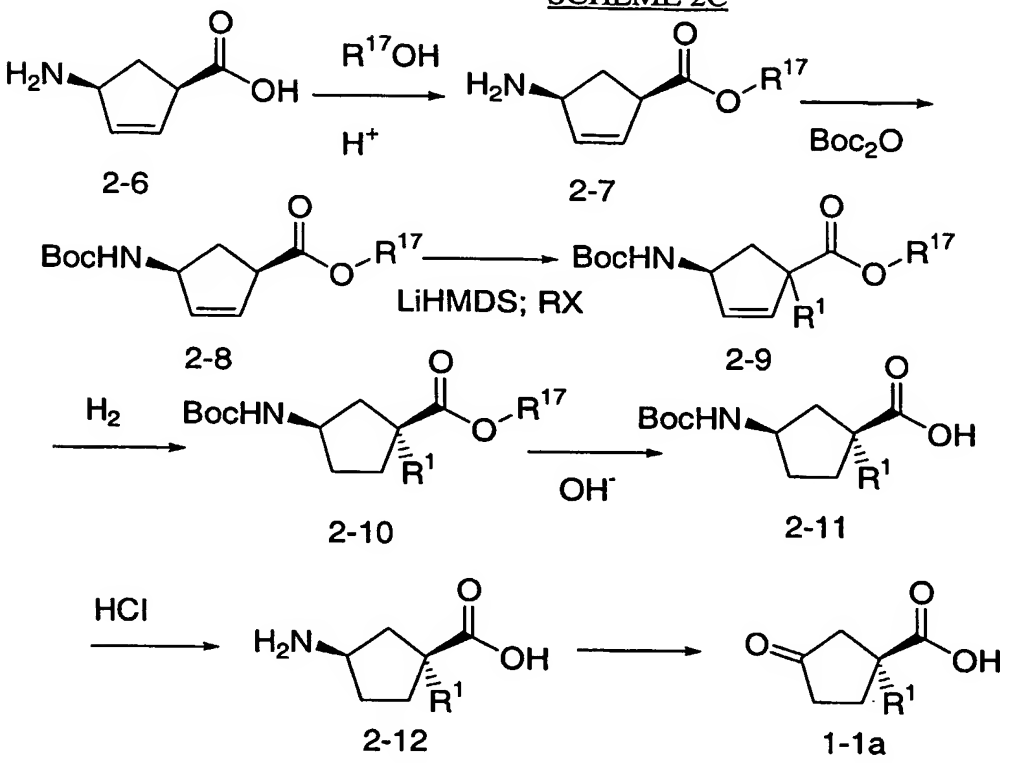
SCHEME 2B



According to Scheme 2C, chiral ketoacid intermediate 1-1a can be prepared starting from commercially available optically pure amino acid 2-6. Protection of the carboxylic acid group can be achieved in a variety of ways. When R^{17} is methyl, esterification can be accomplished by treatment with methanol in the presence of an acid catalyst such as HCl. Treatment with Boc_2O results in protection of the amine group of 2-7. Stereoselective alkylation of ester 2-8 with an alkylating agent such as an alkyl chloride, bromide or iodide in the presence of an appropriate base such as lithium bis(trimethylsilyl)amide, produces intermediates 2-9. Hydrogenation in the presence of a catalyst such as Pd/C affords 2-10. Hydrolysis of the ester to give 2-11 can be achieved under standard conditions depending on the R^{18} group. For example, when R^{17} is methyl (methyl ester), hydrolysis can be accomplished by treatment with a base such as sodium hydroxide, lithium hydroxide, or potassium hydroxide, with or without heating. The Boc protecting group can be removed under standard acidic conditions, such as with HCl in a solvent such as dioxane, or with TFA. Oxidation of 2-12 to give 1-1a (as a single stereoisomer if constituent R^1 is achiral, or as a mixture of stereoisomers if constituent R^1 has a chiral center)

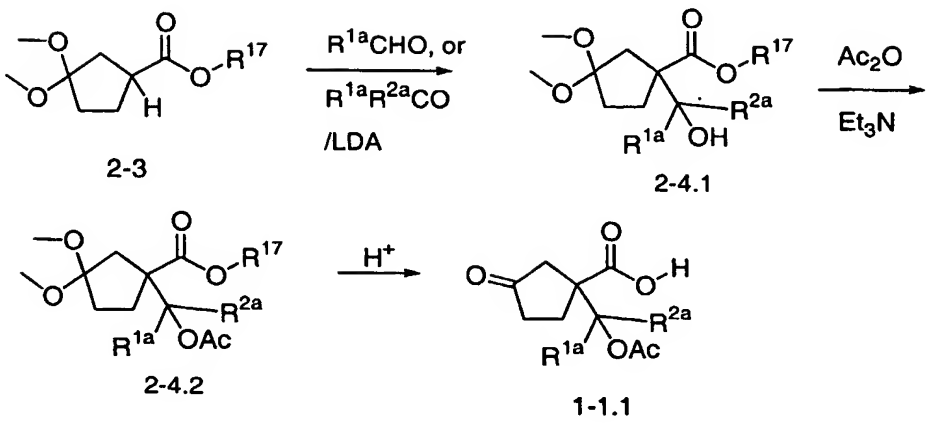
can be achieved in several ways, including by treatment with NBS, followed by treatment with sodium methoxide.

SCHEME 2C



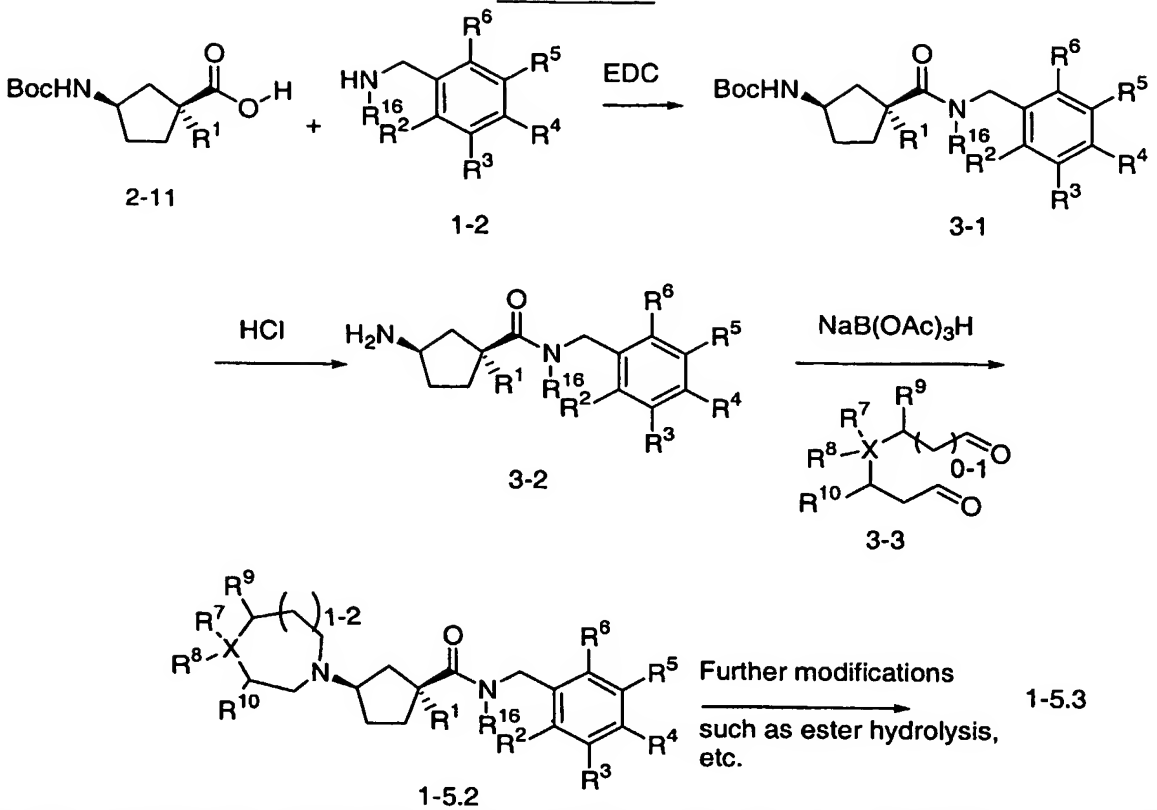
The enolate generated from ester 2-3 (R^{17} being a benzyl or tert-Butyl group) in the presence of a strong base such as lithium diisopropylamide can be reacted with aldehydes ($R^{1a}CHO$) or ketones ($R^{1a}R^{2a}CO$) to produce the appropriate hydroxyalkyl substituted intermediates 2-4.1 as indicated in Scheme 2D. The resulting hydroxy group can be protected in various ways, including by treatment with acetic anhydride in the presence of a base such as triethylamine to give intermediates 2-4.2. Once again the ester protecting group is removed under conditions suitable for the particular protecting group. In the case of the tert-butyl esters (R^{17} is t-butyl), deprotection is achieved under acidic conditions. The latter usually induces cleavage of the acetal protecting group as well, and the keto acids 1-1.1 can be prepared this way in an one-pot procedure. Their conversion to the final modulators of chemokine activity 1-9 can be achieved as described previously, with minor modifications to accommodate the protected hydroxy in 1-1.1.

SCHEME 2D



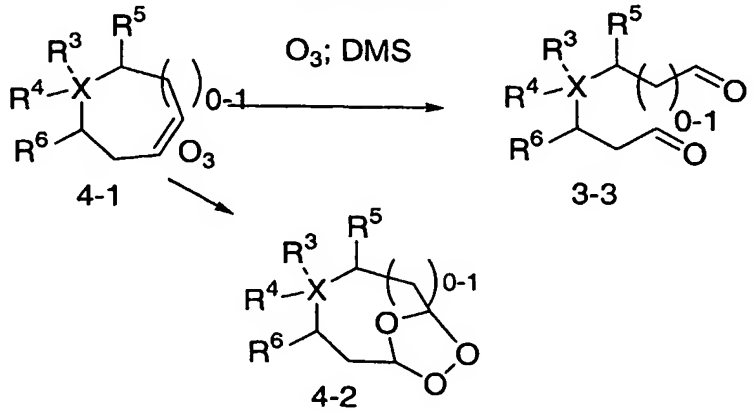
Another principal route for the synthesis of chemokine receptor modulators is depicted in Scheme 3. According to this route, intermediate 2-11 (described in Scheme 2C) is condensed with amine 1-2 (described in Scheme 1) using a peptide coupling reagent such as EDC to give 3-1. The Boc protecting group is removed under standard conditions such as with HCl in a solvent such as dioxane followed by treatment of the resulting amine 3-2 with a dialdehyde 3-3 in the presence of a reducing agent such as sodium triacetoxyborohydride leads to a double reductive alkylation sequence with concomitant cyclization to give 1-5.2. In accord with Scheme 1, further modifications, such as hydrolysis of an ester group present within 1-5.2 can be effected to give new chemokine receptor modulators 1-5.3.

SCHEME 3



One way of preparing dialdehydes 3-3 is outlined in Scheme 4. According to this route, a (hetero)cycloalkene 4-1 is oxidatively cleaved with, for example, ozone followed by reduction with dimethylsulfide, to give the dialdehyde. Alternatively, in place of the dialdehydes 3-3 the intermediate ozonides 4-2 can themselves be used directly in the double reductive amination reaction leading to 1-5.2.

SCHEME 4



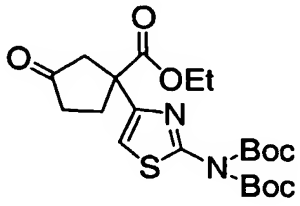
In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

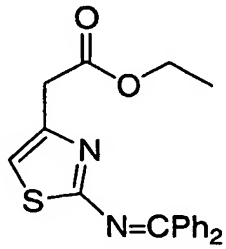
Concentration of solutions was generally carried out on a rotary evaporator under reduced pressure. Flash chromatography was carried out on silica gel (230-400 mesh). NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA) saturated aqueous (sat'd), room temperature (rt), hour(s) (h), minute(s) (min).

The following are representative Procedures for the preparation of the compounds used in the following Examples or which can be substituted for the compounds used in the following Examples which may not be commercially available.

INTERMEDIATE 1

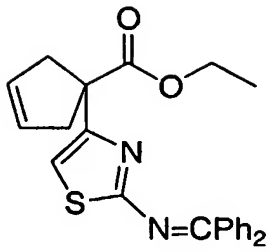


Step A



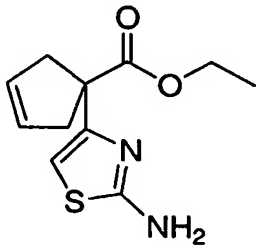
A neat mixture of 54 g (0.29 mole) ethyl (2-aminothiazol-4-yl)acetate and 50 g (0.28 mole) benzophenone imine was stirred at 190 °C for 5 h and then cooled to room temperature and diluted with 100 mL of DCM. The entire mixture was transferred onto a silica gel column and eluted with 20% EtOAc/Hexane. The title compound was obtained as light-yellow solid (70 g, 69% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 3H), 3.74 (s, 2H), 4.15 (q, 2H), 6.87 (s, 1H), 77.25-7.86 (m, 10 H); Mass Spectrum (NH_3-CI): m/z 351 (M+1).

Step B



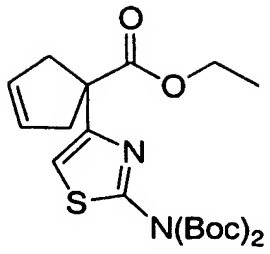
To a mixture of 35 g (0.10 Mole) of the Schiff base ester (Step A above), cis-1,3-dichloro-2-butene (13 mL, 0.11 Mole) in 500 mL of DME at room temperature was added in multiple portions solid NaH (60% oil, 10.0 g, 250 mmol). The resulting mixture was stirred for 2 days, poured into 2000 mL of ice-water, and extracted with 1500 mL of ether. The ether layer was washed with water (3 x 500 mL), dried over Na_2SO_4 and evaporated. Flash chromatography (Silica Gel, 5% EtOAc/Hexane) afforded the title compound as an oil (24 g, 59%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, 3H), 2.87 (d, 2H), 3.19 (d, 2H), 4.14 (q, 2H), 5.29 (s, 2H), 6.71 (s, 1H), 7.26-7.81 (m, 10H). Mass Spectrum (NH_3-CI): m/z 403 (M+1).

Step C



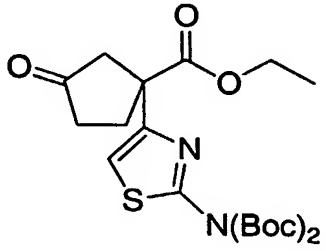
24.0 g (59 mmol) of the cyclopentene Schiff base (Step B above) was dissolved in 100 mL of 4 N HCl/dioxane. After 1 h, 1.8 mL of water was added. The mixture was stirred for 3 h, evaporated to dryness. The residue was dissolved in 100 mL of DCM and 15 mL of DIEA was added. The entire mixture was poured onto a silica gel column, eluted with 20% EtOAc/Hexane to remove benzophenone, then eluted with 40% EtOAc/Hexane to give the title compound as a light yellow solid (12.0 g, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, 3H), 2.79 (d, 12H), 3.15 (d, 2H), 4.13 (q, 2H), 5.66 (s, 2H), 5.82 (wide, 2H), 6.19 (s, 1H).

Step D



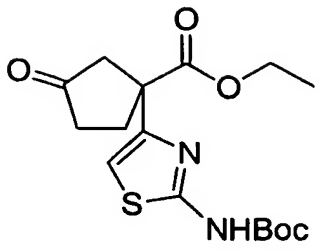
A mixture of 12 g (50 mmol) of the aminothiazole (Step C above), 28 g (130 mmol) of di-tert-butyl dicarbonate and 0.6 g of DMAP in 250 mL of DCM was stirred overnight, and evaporated. The title compound (21.0 g, 96%) was obtained as a yellow oil after flash purification on silica gel (10% EtOAc/Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, 3H), 1.49 (d, 18H), 2.88 (d, 2H), 3.18 (d, 2H), 4.13 (q, 2H), 5.65 (s, 2H), 6.83 (s, 1H). Mass Spectrum (NH_3-CI): m/z 439 (M+1).

Step E



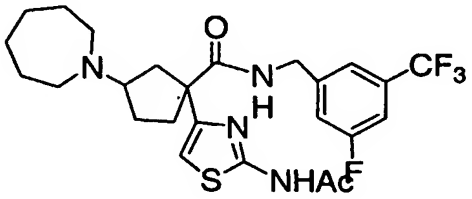
To a solution of 13.1 g (30 mmol) of the ester (Step D above) in 50 mL of anhydrous ether at –78 °C was added dropwise a solution of BH_3.DMS in THF (14 mL, 24 mmol). The cooling bath was removed and the mixture was stirred at room temperature for 3 h, diluted with 250 mL of DCM, added 25 g of sodium acetate and 55 g of PCC. The mixture was stirred overnight. The entire mixture was poured onto a silica gel column and eluted with in 10 % EtOAc/Hexane and then 30% EtOAc/Hexane. Two components were obtained. The fast-eluted isomer (yellow oil, 6.0 g) was identified as the title compound.. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, 3H), 1.50 (s, 18H), 2.33 (t,2H), 2.42-2.70 (m, 2H), 2.78-3.10 (dd, 2H), 4.18 (q, 3H), 6.88 (s, 1H). Mass Spectrum (NH_3-CI): m/z 455 (M+1).

Step F

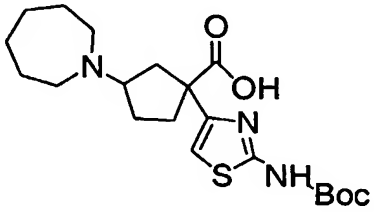


The slow-eluted component from the flash chromatography in the synthesis of the cyclopentene (Step E above) was proved to be the title compound (gummy material, 1.80 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, 3H), 1.46 (s, 9H), 2.27 (3, 2H), 2.38-2.62 (m,2H), 2.64-3.00 (dd, 2H), 4.11 (q, 2H), 6.66 (s, 1H). Mass Spectrum (NH_3-CI): m/z 355 (M+1).

EXAMPLE 1

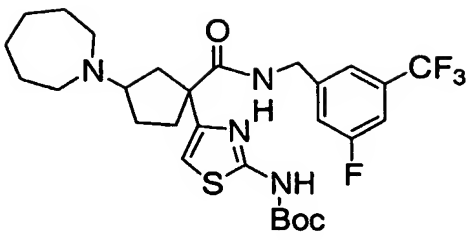


Step A



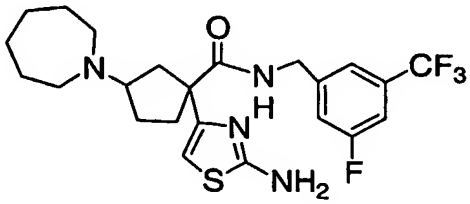
To a solution of the ketone (2.37 g, 5.22 mmol) in THF (25 mL) was added hexamethyleneimine (600 μL, 5.32 mmol) followed by $NaBH(OAc)_3$ (3.50 g, 15.7 mmol). The reaction was stirred at room temperature overnight. Methanol (10 mL) and water (1 mL) was then added to give a clear solution. LiOH (1.00 g) was then added. After stirred at room temperature for another 16 hours, the reaction was acidified by the addition of AcOH (3 mL). 1/4 of this mixture was purified on reverse phase HPLC to give 400 mg of the desired acid as a mixture of cis/trans isomers (75% yield based on the crude materials used in the purification). LC-MS for $C_{20}H_{32}N_3O_4S$ [M+H$^+$]: calculated 410.20, found 410.25.

Step B



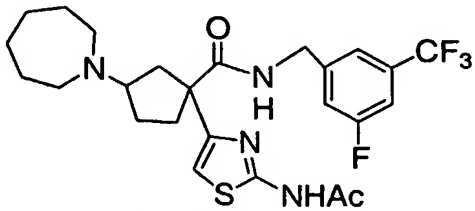
To a solution of the acid from step A (80 mg, 0.196 mg), 3-fluoro-5-(trifluoromethyl)benzylamine (35 μL, 0.235 mmol), DMAP (5.0 mg) and DIEA (70 μL, 0.402 mmol) in CH_2Cl_2 (2 mL) was added EDC (56 mg, 0.29 mmol). The reaction was stirred at room temperature for 10 hours before concentrated and purified by reverse-phase HPLC to give the desired product (70 mg, 61%) as a 4/1 mixture of cis/trans isomers. LC-MS for $C_{28}H_{37}F_4N_4O_3S$ [M+H$^+$]: calculated 585.24, found 585.2.

Step C



The product of step B (60 mg, 0.102 mmol) was taken in TFA (2.5 mL). This clear solution was stirred at room temperature for 40 minutes before concentrated to dryness *in vacuo*. This oil was dissolved in 2 mL of 4 N HCl in dioxane and then concentrated to dryness *in vacuo* to give the desired product as a white solid (50 mg, 88%). LC-MS for $C_{23}H_{29}F_4N_4OS$ [M+H$^+$]: calculated 485.19, found 485.15.

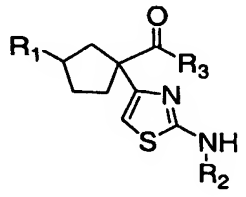
Step D

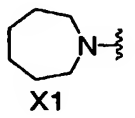
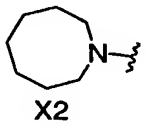


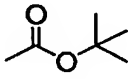
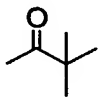
To a solution of the product from step C (100 mg, 0.180 mmol) in CH_2Cl_2 (2 mL) was added pyridine (500 μL, 4.16 mmol) followed by Ac_2O (133 μL, 1.04 mmol). The reaction was stirred at room temperature for 2 hours before quenched by the addition of methanol (0.5 mL). The

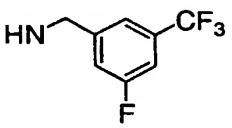
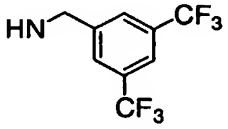
resulted mixture was purified on reverse-phase HPLC to give the desired product as a mixture of cis/trans isomers. LC-MS for $C_{25}H_{31}F_4N_4O2S$ [M+H$^+$]: calculated 527.20, found 527.15.

Examples 2-12 were synthesized according to the procedure described in Example 1 using various substituents at R1, R2 and R3 as shown in the table below. The components were either commercially available or synthesized according to literature procedures.



R1  X1  X2

R2  H  

R3  Y1  Y3

Example	R1	R2	R3	Molecular Formula	Calc. MW	Found [M+H]$^+$
2	X1	Boc	Y1	C28H36F4N4O3S	584.24	585.20
3	X1	Boc	Y2	C27H36F3N5O3S	567.25	568.25
4	X2	Boc	Y1	C29H38F4N4O3S	598.26	599.30
5	X1	H	Y1	C23H28F4N4OS	484.19	485.15
6	X2	H	Y1	C24H30F4N4OS	498.21	499.15
7	X2	H	Y3	C25H30F6N4OS	548.20	549.20
8	X1	Ac	Y1	C25H30F4N4O2S	526.20	527.15

9	X2	Ac	Y1	C26H32F4N4O2S	540.22	541.10
10	X1	Ac	Y3	C26H30F6N4O2S	576.20	577.20
11	X2	Ac	Y3	C27H32F6N4O2S	590.22	591.20
12	X2	Piv	Y3	C30H38F6N4O2S	632.26	633.2